Sepsis-Associated Acute Kidney Injury: Making Progress Against a Lethal Syndrome

6

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6.1 Introduction

What we think, we become—Gautama Buddha.

Sepsis and acute kidney injury (AKI) are epidemic problems in hospitalized patients. Together, sepsis-associated AKI (S-AKI) is a syndrome carrying lethal downstream sequelae. Epidemiologic data indicate sepsis increases the rate of AKI, AKI increases the rate of sepsis, and together, S-AKI increases the rates of morbidity and mortality significantly above baseline. Evidence from small and large biological models of sepsis and AKI describes considerable overlap between the pathophysiologic drivers of both processes. These are recapitulated in models of S-AKI. Unfortunately, a significant proportion of published literature focuses either on associative population data or the complex minutiae underpinning the mechanistic drivers of the syndrome. Very few reports attempt to connect the dots and describe how the bench and the bedside can be understood together and even fewer describe how this connection can be leveraged. This chapter takes a progress-driven approach to S-AKI. The existing perspective and *status quo* of epidemiology, understanding of pathophysiology, diagnostic tools, and management options will be described. Assumptions regarding S-AKI will be discussed. The chapter will then describe how these assumptions should be challenged and how challenging opens the door to making actual progress. Using collaboration, innovation, and a more contemporary approach, it will be possible to refine and improve the understanding of disease epidemiology, untangle the syndrome pathophysiology, increase the sophistication of diagnostics, and facilitate the targeting of putative therapy.

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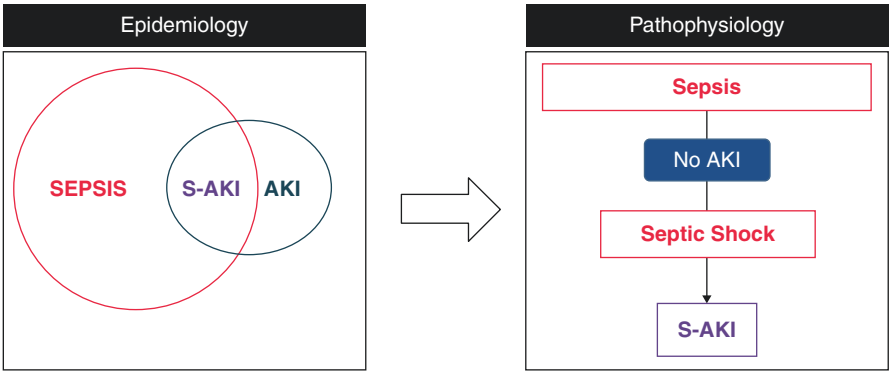

Fig. 6.1 Current perspective—epidemiology drives physiology. The status quo for how sepsis-associated acute kidney injury (S-AKI) is depicted above. The epidemiology for the disease process is entirely contained within the scope of both sepsis and AKI. Sepsis is the predominant driver of AKI. The findings clinically drive research strategy in the laboratory, where the pathophysiology is studied by examining the kidney in models of sepsis and septic shock

The understanding of how sepsis-associated AKI occurs, is diagnosed, and is managed has been fueled by clinical incidence and prevalence data. Epidemiology has driven, and biased, study of pathophysiology and impacted the ability to identify options for effective management (Fig. 6.1).

6.1.1 Existing Perspective: Epidemiology

The incidence of sepsis or septic shock has increased over the past two decades. Prior to the most recent reports, the population incidence for sepsis was 22 to 240 per 100,000 and 13–300 per 100,000 for severe sepsis [1]. A 22-year retrospective analysis of hospitalization records in the United States found an 8.7% annual increase for sepsis diagnosis [2]. The incidence of severe sepsis from 2004 to 2009 demonstrated an average annual increase of 13% [3]. Global estimates suggested significant associations with sepsis encompassing all aspects of ICU-related morbidity—including prolonged length of stay, ventilation, secondary infections, and mortality along with long-term survival [4–7]. Meanwhile, integration of consensus AKI criteria definitions of RIFLE, AKIN, and most recently KDIGO has facilitated identification of AKI incidence in intensive care unit (ICU) settings. Adult reports ranged between 16 and 67% [8–18] while scattered pediatric ICU studies reported similarly high incidence rates [19, 20]. Like sepsis, mounting evidence has indicated a rise in AKI incidence. In a large 10-year cohort that included more than 90,000 from more than 20 ICUs, AKI incidence increased by 2.8% per year [10]. A longitudinal pediatric study demonstrated a parallel rise in reported AKI incidence [21]. Also, like sepsis, the presence of AKI has been consistently associated with increased morbidity and mortality for both adults and children. The epidemiologic data for AKI has created paradigm shift, suggesting people are no longer just dying with AKI, but *from* AKI [22].

Sepsis-associated AKI (S-AKI) occurs at a high incidence rate in critically ill patients. A large adult ICU study from Australia and New Zealand identified S-AKI in 11.7% of 120,123 patients [23]. Sepsis is the leading predominant condition associated with AKI; the BEST kidney study reported an AKI incidence of 5.7% in 29,000 patients with sepsis being the highest associated etiology (47.5%) [24]. Analysis of 276,731 admissions to 170 adult critical care units of the Intensive Care National Audit and Research Center in the United Kingdom (ICNARC) identified concurrent sepsis and AKI in 8246 ICU admissions in first 24 h [25]. Meanwhile, in another cohort, AKI was present in 17.7% of 722 patients admitted to an ICU specific for infectious disease [26]. Infection was identified as an independent predictor of AKI in large pediatric cohort of 2106 critically ill children (18% AKI incidence) [27]. A 10-year longitudinal retrospective analysis reported sepsis as a leading cause of AKI in 180 children [28]. A prospective multicenter study from Turkey reported sepsis as a leading cause of AKI in 18% of 472 patients [29]. Similarly, sepsis was an independent risk factor for the development of AKI in a retrospective observation study from India [30]. Thus, S-AKI is a global health care issue in adults and children.

Sepsis-associated AKI is strongly associated with a poor prognosis. Observational studies consistently report significantly worse outcome with S-AKI versus non-septic AKI or sepsis alone. Length of stay (LOS) is longer in patients with S-AKI versus AKI without sepsis or sepsis alone. Septic patients developing AKI were found to have twice the duration of ICU stay compared to septic patients without AKI [23]. Similar findings from a larger cohort found S-AKI patients to have longer ICU and hospital stay compared to non-septic AKI or sepsis alone. Recovery of renal function is similar for patients with S-AKI versus AKI without sepsis. Complete renal function recovery occurred in 95.7% of 315 S-AKI patients, with mean time for complete recovery of 10.1 ± 8 days [31]. Both ICU and inhospital mortality were significantly higher for patients with S-AKI compared to AKI without sepsis (ICU mortality: 19.8 vs. 13.4% and inhospital mortality: 29.7 vs. 21.6%). Mortality was significantly higher in S-AKI for AKI-AKIN stage 3 (64.1%) compared with AKI-AKIN stage 1 (34.6%). Very little data have been published focused on S-AKI in pediatrics. A small, single-center study identified a mortality rate of 57.1% in children with septic shock and acute renal failure compared to 6.7% in septic shock without ARF [32]. Prior to the past 3 years, extrapolations are made from adult studies and applied to children and neonates.

In total, the epidemiology of S-AKI has suggested that the injury is entirely a subset of sepsis and AKI (Fig. 6.1).

6.1.2 Existing Perspective: Pathophysiology

Current understanding of S-AKI pathophysiology is based on the predominant systemic effects (and understanding) of septic shock [33, 34]. The argument created is that the disease process in S-AKI is linear, occurring in stepwise series fashion from sepsis to septic shock to S-AKI (Fig. 6.1). Understanding sepsis, therefore, would facilitate a complete understanding of S-AKI.

Sepsis is, in simplistic terms, an infection leading to a dysregulated host immune response. This dysregulation is manifest by aberrancies in pro- and anti-inflammatory mediators. Septic shock is the sequelae of sepsis, wherein a host suffers from the imbalance of oxygen supply and demand. Oxygen demand increases as utilization can increase at the tissue level and supply decreases secondary to issues with cardiovascular efficiency. The relationship between cardiac output and systemic vascular resistance in sepsis is, however, highly variable by age. Adult septic shock is generally characterized by high cardiac output and low systemic vascular resistance (SVR), also known as "warm shock." Conversely, most children with septic shock have low cardiac output and high SVR, or "cold shock" [35]. Myocardial function varies considerably in children—and varies from infancy to adolescence. Regulation of myocardial excitation-contraction coupling is incomplete in the neonatal period and is further characterized by a relatively greater sensitivity and dependence of neonates on calcium and β-adrenergic stimuli compared with older children or adults. Endothelial disruption is a hallmark of sepsis in adults. Alterations in adult endothelial homeostasis include leukocyte adhesion, vasodilation, creation of a pro-coagulant milieu, and loss of the capillary brush border. As endothelium covers the lining of essentially all vital organs, these perturbations in sepsis lead to end-organ effects secondarily. Epithelial changes also occur in sepsis and organ epithelial tissue (e.g., lung and gut epithelia) becomes more friable and leaky. Organ epithelia and the vascular endothelium in children is highly reactive and, in an effort to compensate for changes in cardiac output, switches rapidly to a vasoconstricted or high resistance state in septic shock [35]. Due to both the fragility of the myocardium and vascular integrity, children are much more vulnerable to the end-organ effects of shock from sepsis than adults.

Dysregulation of the innate and adaptive immune responses in sepsis leads to injury. The dysregulation is not consistent from patient to patient and neither is the degree of injury. Sepsis leads to wide variations in the host immune response, with early pro-inflammatory effects predominating and later predominating anti-inflammatory or immunosuppressive effects. Both cytokines and chemokines involved in direct inflammation mediation or cellular recruitment are dysregulated in sepsis. End-organ effects of sepsis are highly variable based on age of the patient and degree of systemic comorbidities. Adults with chronic heart disease, diabetes, and autoimmune or immunosuppressive conditions are highly susceptible to damage from inflammatory dysregulation. While children with similar comorbidities are also at higher risk, the average child has a baseline increased risk. Maturation of the immune system, both adaptive and innate, is incomplete until toddler age, explaining why neonates and children have marked heterogeneity in inflammatory response. In general, inflammatory dysregulation (particularly the immunosuppressive effects of sepsis) plays a greater role in septic shock in children than in adults [36]. Taken together, sepsis leads to host homeostatic imbalance starting from the microscopic and cellular level, cascading into significant host dysregulation with deleterious end-organ impact. Significant differences exist in the pathophysiology of sepsis between adults, children, and neonates.

Per traditional thinking, S-AKI is the net result of septic shock on the kidneys. As sepsis progresses, systemic vascular resistance shifts from low to high, spurred by neurohormonal-mediated vasoconstriction, thereby heightening end-organ vascular

tone. This model may not be entirely recapitulated in young patients. Unfortunately, an age-specific adjustment (or model), appropriate for cardiovascular effects on the kidney in sepsis, has not been reported. Inflammation of the nephron, hypoxic and/or oxidant stress, cytokine and chemokine driven direct tubular injury, and tubular and mesenchymal apoptosis have all been linked in the process of S-AKI. Strong associations exist between pro-inflammatory cytokines TNF-α, IL-6, and IL-10 and S-AKI. Additionally, interactions between pathogens and pathogen receptors such as toll-like receptors (TLRs), pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) have all been implicated in S-AKI [37]. Pro-inflammatory cytokines, DAMPs, and PAMPs directly and indirectly induce tubular damage, proximal to renal tubular epithelium, and contribute to loss of function. Oxidative stress is associated with renal tubular damage. Mainly secondary to ischemia-reperfusion or neutrophil burst, oxidative stress can affect the balance of cell survival, arrest, necrosis, or programmed cell death (apoptosis). Bioenergetic failure, mitochondrial arrest, occurs during sepsis and has been implicated in S-AKI [38]. The combination of findings is a laundry list of putative intracellular mechanisms that induce damage independently and synergistically. How the pieces fit together remains a mystery [39]. Even more of a mystery is how the pieces fit together differently for a child versus an adult. Despite the uncertainty, the "given" is that S-AKI pathophysiology is driven in a linear manner by sepsis, is a natural consequence of septic shock, and leads to severe, persistent tubular cell death.

6.1.3 Existing Perspective: Diagnostics and Management

To date, no effective singular therapy for AKI exists, so management of S-AKI is predicated on recognition of AKI and management of sepsis. What follows is management "in series" (Fig. 6.2). Standardized criteria (RIFLE, pRIFLE, AKIN, and KDIGO) have facilitated description of AKI epidemiology based on creatinine and urine output changes from baseline. Therefore, recognition of S-AKI is also based on these parameters. Some of these data were discussed earlier. In the context of sepsis, many clinicians will institute the parameters of goal-directed therapy

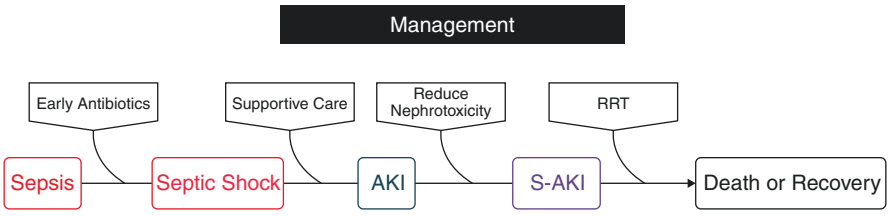

Fig. 6.2 Current perspective—management in series. The status quo for how sepsis-associated acute kidney injury (S-AKI) is treated is depicted above. Sepsis is managed initially and support is escalated when shock is manifest. When end-organ effects on the kidney are detected by changes in creatinine, kidney-specific "management" is incorporated. Renal replacement therapy is incorporated as a "last line" intervention in the case of life-threatening S-AKI

including stabilization and optimization of fluid status, mean perfusion pressure, and oxygen delivery. Source control of the infectious agent (s) is paramount as delayed antimicrobial therapy is associated with increased mortality in septic shock, every hour without coverage increases mortality by nearly 10% [40]. Randomized controlled trials testing the effects of other interventions have failed to demonstrate consistent efficacy in sepsis. When AKI is recognized in the context of sepsis, management of sepsis is combined with adapted KDIGO AKI guidelines to include: minimization of unnecessary nephrotoxins and adjustment of nephrotoxic medications based on renal clearance (as estimated by creatinine), conservative resuscitation (with regards to administration of intravenous fluids), and consideration of renal replacement therapy. Indications for the initiation of RRT in adult patients with S-AKI have included "life-threatening AKI complications" and "aberrant fluid balance" [41] but RRT therapy for critically ill septic patients is controversial. Timing and modality are uncertain although evidence suggests initiation of support before significant fluid accumulation may be associated with improved patient outcomes. Additionally, recent data have suggested that initial support with CRRT may better facilitate recovery of kidney function to RRT independence and reduce the long-term risk of incident CKD [42, 43]. Despite early data by Ronco et al. suggesting potential benefit from higher intensity dose dialysis (35–45 mL/kg/h) [44], subsequent evidence from two large multicenter randomized trials (RENAL: randomized evaluation of normal versus augmented level renal replacement therapy and ATN: Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study) showed no added benefit of higher intensity-dose RRT compared to lower intensity-dose RRT with fewer metabolic complications [45, 46]. Additionally, in both the RENAL and ATN studies, there were no significant difference in the odds ratios (OR) for mortality in patients with sepsis who received higher versus lower intensity RRT. In the RENAL study, high versus low intensity RRT conferred an OR for death by 90 days of 0.84 (0.62–1.12) while in the ATN study intensive versus less intensive therapy conferred an OR for death at 60 days of 1.19 (0.88–1.62) [45, 46]. Although some data suggest that CRRT might have potential immunomodulatory effect in sepsis, the IVOIRE study investigated high volume hemofiltration in septic shock patients with AKI and found no survival or clinical benefits [47]. Very little published data discusses the diagnostics or management of S-AKI in children.

6.1.4 Interlude—Challenging the Givens

When there is a problem, always identify and evaluate your underlying assumptions that may be contributing to the problem or preventing you from seeing the problem clearly—Elizabeth Thornton

In total, the existing paradigm of sepsis-associated AKI is driven by the influence and understanding of sepsis. Epidemiology of sepsis governs the epidemiology of S-AKI. Sepsis pathophysiology drives the pathophysiology of S-AKI. Diagnostics are based on recognition of sepsis and signs of severe sepsis or septic shock while creatinine change is used to identify AKI in the context of sepsis unless fluid accumulation becomes clinically significant. Management of S-AKI is governed

Table 6.1 Assumptions to challenge for sepsis-associated AKI

• S-AKI is the result of a construct in "series"
– Sepsis is the pathophysiologic driver of S-AKI
– S-AKI morbidity and mortality is driven by the sepsis
– S-AKI epidemiology is contained entirely within sepsis epidemiology
– S-AKI management is governed by the principles of sepsis management
• Creatinine is a sufficient marker of incipient S-AKI and to direct guide S-AKI management
• "Life-threatening" AKI is an indication for initiation of RRT
• The phenotype of S-AKI is similar in adults, children, and neonates

primarily by the management of sepsis (source control, optimization of oxygen delivery and utilization) while the management AKI in S-AKI approximates the Hippocratic Oath ("*primum non nocere*") applied to the kidneys. Adults and children and neonates are not differentiated with regards to diagnostics or management strategies. Meanwhile, outcomes for these patients (all ages) are ominous and significantly worse both in the short and long term compared to patients without sepsis or AKI, with sepsis and no AKI, or AKI and no sepsis. The question that must be asked by all is simply—is the *status quo* adequate? The answer is no.

In order to move past the existing paradigm and the twentieth century approach to S-AKI, "givens" must be challenged, a comprehensive reevaluation must be performed, and innovation must be leveraged (Table 6.1).

6.1.5 Contemporary Approach to Sepsis-Associated AKI

The contemporary approach to understanding sepsis-associated AKI, particularly in children, requires a return to the biology of the syndrome. It is not by accident that the second half of this chapter begins with a discussion regarding pathophysiology. The existing dogma must be challenged. In the text that follows, the central role of the kidney in pathophysiology will be described and a modified view of S-AKI constructed, careful to delineate the findings that can and cannot be extrapolated to pathophysiology in children and neonates. An adjusted understanding of S-AKI epidemiology will be detailed, including newer large, multicenter population data. The necessary approach created will be pathophysiology driving the understanding of epidemiology. A new diagnostic framework will be illustrated—incorporating risk and context and novel biomarker approaches to refine and improve the precision of diagnosis. Finally, the options for management will be shifted to a contemporary, personalized approach, targeting S-AKI phenotypes.

6.1.6 Contemporary Approach: Pathophysiology

The kidney is a central mediator of host homeostasis and aberrant kidney function impacts systemic health. Responsible for not only solute and fluid clearance, the kidney governs vascular stability, neurohormonal response to stress, calcium–phosphorus balance, regulates acid–base control, and modulation of erythropoietin

in states of marrow suppression and/or anemia. Recent evidence from both animal and human models indicates an even more expansive set of distant organ molecular checks and balances controlled by kidney function [48]. Aside from propagating injury in endocrine fashion, that is isolated models of AKI triggering a cascade of localized injury in the glomerulus, renal mesenchyme, and tubular epithelium, AKI models also result in distal organ injury [48, 49]. Isolated models of AKI induce host vasomotor instability secondary to changes in the vascular endothelial response to catecholamines, loss of vascular and epithelial integrity in the lung and brain, myocardial dysfunction by myocyte apoptosis, and aberrant T-cell trafficking [50]. In two-stage models, a primary AKI leads to a far worse secondary injury phenotype (sepsis, lung injury, hemorrhagic shock). In a majority of these models, the distal organ effects on the host occur before changes in creatinine or urine output and end-stage renal failure—pointing to early and notably *independent* effects of AKI on the host. Finally, although not yet studied extensively, pediatric-aged animal models of AKI demonstrate a different injury pattern than adult-aged models [51]. The cumulative evidence suggests not only does an isolated injury to the kidney trigger a continuous propagation of renal injury in multiple areas of the nephron but also impacts host homeostasis, varied by age. AKI contributes to adverse systemic pathophysiology including propagation of infections and sepsis [52].

The effects of sepsis on renal perfusion in the kidney vary based on context. Sepsis inconsistently leads to aberrant renal perfusion. Multivariate analysis in a systematic review of 159 animal studies, a majority of which (62%) reported decreased renal blood flow during sepsis, demonstrated that RBF is only predicted by sepsis induced changes to cardiac output (i.e., low cardiac output) [53]. In an ovine model of *E. coli* sepsis, sepsis conferred a period of *hyper-dynamic* RBF for 48-h after *E. coli* infusion, attributed to increased cardiac output and renal vasodilatation [54]. Overall RBF seems to be less contributory to renal perfusion during sepsis unless cardiac output is affected. This dynamic has not been studied in relationship to host age, however. As described earlier, pediatric septic shock is more often associated with low cardiac output (myocardial stun) than adult septic shock. Further decreasing age is associated with less myocardial functional reserve and less myocyte actin-myosin cross-bridging, ultimately leading to higher myocardial oxygen consumption for the same level of myocardial demand. Neonates are particularly vulnerable to the effects of septic shock and impaired end-organ effects are commonly seen in the neonate (necrotizing enterocolitis, cerebral ischemic-hypoxic injury in meningitis). Intravascular capacitance, combining both the amount of functional vascular reserve and endothelial integrity, is compromised in pediatric models of sepsis. Together, the hemodynamic effects of sepsis on the kidney in the younger patient may actually be more contributory to S-AKI than in adults. An adjudicated understanding of renal perfusion in sepsis needs to be taken—in adults, the primary effects on the kidney occurring during the early stages of sepsis may not be related to hemodynamics, while in children and neonates, the effects on renal perfusion may be more significant.

The contribution of inflammation in the propagation of AKI during sepsis is highly variable from host to host. In fact, when attempting to understand the

rationale behind the long list of failed sepsis therapeutics treating inflammation (e.g., steroids) a major rationale is now absent or insufficient patient stratification. Therefore, a substantial amount of data describes serum-based sepsis genotypes or endotypes in both adults and children [55, 56]. These data suggest both from the laboratory and from the bedside that distinct patient phenotypes correspond with different pathophysiology and different patient outcome. These findings also support the hypothesis that the influence of sepsis-mediated inflammation on renal function and tubular integrity may also be highly variable. The variability in turn should lead us to challenge the dogma regarding S-AKI. Tubular necrosis, traditionally cited as the major cellular switch for injury, is not supported by the available experimental evidence [57]. Renal tubular *apoptosis* may be a significant contributing mechanism of injury in SA-AKI [58]. In a side-by-side experimental comparison of murine models of SA-AKI versus ischemia-reperfusion (using cecal ligation puncture model), renal cell apoptosis was more prominent on renal histology in the SA-AKI mice with minimal tubular injury or inflammation [58]. In a porcine model of fecal peritonitis, renal tubular cells demonstrated vacuolization and injury to cellular brush borders but no evidence of necrosis [59]. In a model of lipopolysaccharide (LPS) induced endotoxemic AKI, reactive nitrogen species (RNS) and reactive oxygen species (ROS) were over-expressed in the renal cytosolic compartment, implicating mitochondrial and oxidative dysfunction during sepsis. Direct bacterial instillation leads to a polymicrobial inflammatory response—varied by organism used in the slurry. The net result is the importance of limiting extrapolation, as the type of inflammatory dysregulation depends on the type of sepsis model used. Genetic predisposition to injury is also varied in animals secondary to selective inbreeding, an allelic characteristic obviously not present in the majority of available human data [60].

AKI and sepsis contribute individually and synergistically to the pathophysiologic derangements evident in patients with S-AKI. Sepsis can drive AKI, but AKI can also drive sepsis (Fig. 6.3). Different aspects of each drive S-AKI, and importantly these vary from patient to patient. Additionally, S-AKI may actually be a distinct clinical entity from both sepsis and AKI individually, displaying a unique genetic, proteomic, and phenotypic signature. Finally, the drivers of S-AKI pathophysiology in adults should not be assumed to be consistent in children and neonates. The pathophysiology of S-AKI in the pediatric patient is unique as the pathophysiology of both sepsis and AKI in children is unique. Very little formalized and focused data describes the pathophysiology of S-AKI in a pediatric patient or young animal models, but this is essential to properly characterize and ultimately treat these patients.

6.1.7 Contemporary Approach: Epidemiology

Context must be incorporated to understand the epidemiology of sepsis-associated AKI. The varied pathophysiology of sepsis would suggest that stratification systems for studying the epidemiology of S-AKI are needed. Not all sepsis-associated

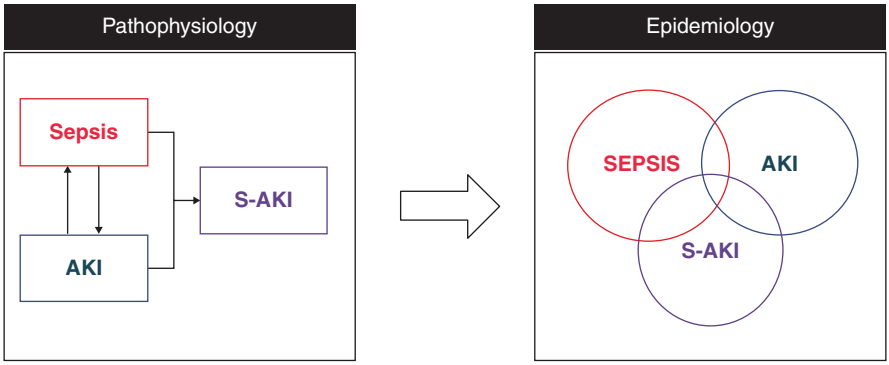

Fig. 6.3 Modern approach—physiology drives epidemiology. Recent evidence indicates that sepsis drives acute kidney injury (AKI) but AKI also drives sepsis. They synergistically can lead to sepsis-associated AKI (S-AKI). This appreciation should lead us to examine newer, large datasets in varied populations from the perspective of S-AKI as perhaps its own unique entity. S-AKI remains an overlap with sepsis and AKI but perhaps there are aspects of S-AKI unique and separate from either of the two processes. Genomic, proteomic, and phenotypic evidence support this hypothesis

AKI is created equal! Risk factors for AKI both in adults and children have been identified. Using these risk factors, a parallel to Prinzmetals' angina for identification/prediction of acute coronary syndrome has been developed for AKI. Named "renal angina," Chawla and Goldstein identified the risk factors associated with the development of severe AKI. Importantly, the risk criteria were dichotomized into adult- and pediatric-specific factors [61]. The importance of the risk stratification system is to identify patients at high risk of severe AKI *early* in their ICU course. The system smooths out the heterogeneity of patient illness severity by creating an objective scoring system (the renal angina index) for the hierarchy of risk [62]. This methodology may enable a more targeted approach to disease diagnostics.

New epidemiologic data may facilitate a more accurate understanding of disease prevalence. A recent worldwide meta-analysis of adult and pediatric datasets identified AKI rates of 21.6% and 33.7%, respectively, and pointed to the need for data from developing nations. The adult AKI-EPI study identified an AKI incidence of 21% in septic patients (vs. 8% in non-septic patients) [63]. The young adult and pediatric AWARE study identified a sepsis prevalence of 14.6% in close to 5000 patients with an AKI incidence rate of 41% in the septic population [64]. The point prevalence SPROUT study identified an AKI prevalence of 21% in septic children with a significant association between severe AKI and death or long-term disability [65]. Finally, the neonatal AWAKEN study reports a sepsis evaluation was less common in babies with AKI (45 vs. 52% in babies without AKI). These large studies multicenter, multinational, collaborative studies on critically ill patients from all agents will facilitate the identification of the true epidemiologic associations with sepsis and AKI as they were designed to study AKI itself rather than AKI being studied in post hoc analysis.

Past and Present	
Time Frame	**Marker**
1960-1980s	Creatinine
1980s-1990s	Creatinine
2000s-2010s	Creatinine
Location	**Marker**
"Renal"	Creatinine
Population Age	**Marker**
Adults	Creatinine
Children	Creatinine
Neonates	Creatinine (or nothing)
Etiology	**Marker**
Ischemic	Creatinine
Septic	Creatinine
Nephrotoxic	Creatinine
Hypoxic	Creatinine
Obstructive	Creatinine
Severity/Progression	**Marker**
Low	Creatinine
High	Creatinine

Future	
Time Frame	**Marker**
2020-2025	Creatinine, Urine Output & Biomarkers
2025-2030	Dynamic Biomarker Combinations
Beyond	Real-time functional tests & endotyping
Location	**Marker**
Glomerulus	Real-time GFR
Tubular Epithelium	Urine biomarker panel
Vasa recta	Renal oximetry
Collecting Duct	Kinetic Urine Output
Population Age	**Marker**
Variable	Age Specific Marker Panels
Etiology	**Marker**
Perfusion/Reperfusion	Real-time GFR
Apoptosis/Necrosis/Autophagy	Biomarker profile
Inflammation/Oxidative Stress	Bioenergetics panel
Chloride Transport	Furosemide Stress Test
Severity/Progression	**Marker**
Low	Negative renal angina
Moderate	Renal angina+/Stable Biomarkers
Progressive/High	Renal angina+/Rising biomarkers

Fig. 6.4 Modernization of diagnostics. The side-by-side comparison of markers for acute kidney injury (AKI) depicts the stark contrast of the past and present construct and the potential of the future. Creatinine is the beginning, middle, and end of diagnostics—even for S-AKI. The future opens the door to possibilities of advances in diagnostics—able to identify the what, when, why, and how of AKI. (*GFR* glomerular filtration rate)

Reliance on creatinine and urine output for diagnostics limits the ability to accurately identify the S-AKI epidemiologic signal. Although imminently useful for standardizing AKI diagnosis for the purposes of getting comparable data across institutions, nations, and populations, these markers have significant, recognized limitations. Aside from being highly varied by age and gender and delayed in response to injury, referenced normative values for creatinine are measured in steady state, a situation diametrically opposed to that for a patient suffering sepsis or AKI. Creatinine itself offers very little insight into the "who, what, where, when, and why" of AKI (Fig. 6.4). Meanwhile, although urine output is a vital sign indicative of a multitude of normal physiologic processes (tubular epithelial integrity and function, juxtaglomerular apparatus sensing, collecting duct aquaporin channel function, sodium–potassium ATPase function, oxygen tension in the vasa recta, just to name a few), it is generically only used to signify "adequate renal perfusion." Current diagnostic strata include urine output but only as a static index in a designated period of time (mL/kg/h). Unfortunately, clinicians generally disregard urine output as a marker of AKI, placing primacy on creatinine changes. The ability to quantify urine output is impeded when priority is placed on removing indwelling bladder catheters (to prevent catheter-associated infections) or when patients wear diapers—obviously a significant problem for the pediatric patient population.

When urine output is not included in the assessment of AKI severity, a significant proportion of AKI is missed. Recent data indicates accounting for UOP in AKI recognition along with creatinine pathways actually identifies a unique subset of AKI patients in adults (vs. either criteria alone) [66]. The AWARE study reports that failure to account for UOP in children misses 20% of AKI cases [64]. Although an imperfect index, failure to even account for urine output in the assessment of AKI is a mistake. A new analysis of creatinine suggests that static measures of creatinine are less indicative of glomerular filtration, instead supporting the case for a kinetic GFR based on change in creatinine over time [67]. In parallel fashion, urine output should be tracked and should likely be tracked in a dynamic state, flow rate change as a function of time.

Novel biomarkers and functional tests of the kidney offer a diagnostic advancement. Novel biomarkers have already demonstrated an ability to identify S-AKI before changes in serum creatinine. Plasma and urine neutrophil gelatinase-associated lipocalin (NGAL) levels were significantly higher at 0, 12, and 24 h in 83 patients with SA-AKI compared with non-septic AKI [68]. Though plasma NGAL increases in patients with sepsis, levels were significantly associated with the renal subscore of the sequential organ failure assessment score (SOFA) in critically ill adults [69]. In a separate, prospective evaluation of 150 septic patients, urinary netrin-1 and KIM-1 were increased within 3 h of admission for patients with AKI [70]. Recent studies demonstrate the ability of NGAL to improve the prediction of severe AKI afforded by the clinical context model of the renal angina index (AUC increased from 0.72 to 0.86, 0.80 to 0.97) [71]. Elevation of E-selectin, typical of inflammatory and endothelial activation, is associated with future AKI in a longitudinal evaluation of patients after sepsis [72]. In a large multicenter study of critically ill adults, cell-cycle arrest markers tissue inhibitor of matrix metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFB7) demonstrated superior discrimination for AKI compared to other novel biomarkers such as NGAL, interleukin-18, liver type-fatty acid binding protein, and kidney injury molecule-1 (KIM-1) (AUC of 0.80 for TIMP-2/IGFBP7 vs. <0.72 for the others) [73]. In this study, the predictive performance of TIMP-2/IGFBP7 for AKI was further increased in patients with sepsis (AUC 0.82). Genomic and proteomic expression also varies in models of AKI [74]. Gene expression in models of S-AKI demonstrates some overlap with both sepsis and AKI models, but also unique characteristics, supporting the notion that S-AKI is an independent, unique disease process.

Functional tests of renal reserve can be performed. The recently described furosemide stress test objectively quantifies the urine flow rate response to a standardized dose of furosemide [75]. The results not only are predictive of AKI progression but also provide information on the health of numerous segments of the kidney (function of the glomerulus, proximal tubule, and loop of Henle are all requisite for furosemide effect). Meanwhile, newer technology being developed may facilitate the tracking of real-time GFR, using fluorescent probes detected by transdermal sensors, real-time GFR monitoring is capable of responding instantaneously to changes in GFR induced by stressors to the kidney [76].

Taken together the field of S-AKI diagnostics requires advancement. The assessment of a patient must begin with a risk assessment, inclusive of patient age. Patients demonstrating greater than low risk merit AKI biomarker assessment and follow up, with functional testing to determine a more precise S-AKI phenotype (Fig. 6.4).

6.1.8 Moving Forward: Management and Targeted Therapeutics

Management of S-AKI can be improved. To date, no singular therapy for S-AKI has been identified and the mainstays of "therapy" are supportive care, removal or reduction of nephrotoxic agents, and renal replacement therapy. As mentioned earlier, RRT initiation is controversial, but post hoc analysis of two large adult studies investigating the effect of "early" initiation of RRT are currently being conducted to determine population-based differences (i.e., sepsis vs. no sepsis) [77–79]. Additionally, ongoing studies (STARRT-AKI) will examine this question further. As S-AKI is a multifactorial process involving a number of molecular switches (programmed cell survival or death, inflammatory and counter inflammatory signaling, hypoxia and oxidative stress to name a few), countering these pathways with novel adjuncts may be beneficial. Targeting the apoptotic pathway with caspase inhibitors and suppressing inflammatory cascades have shown some promising results in experimental models [80, 81]. Other therapeutic agents such as Ghrelin [82], low dose vasopressin [83], adenosine receptor agonists [84], and erythropoietin [85] have shown some renal anti-inflammatory and apoptosis suppressing qualities. Modulation of mitochondrial oxidative phosphorylation through antioxidants also may be of benefit in S-AKI as hypoxia-induced ROS and NOS during sepsis may contribute to renal tubular injury [86]. Recent experimental data demonstrates the potential for the enzyme alkaline phosphatase to improve outcome in S-AKI by favorably modulating the immune response [87].

A novel approach to managing S-AKI will facilitate identification of effective therapy. This approach contrasts starkly with the uniform approach currently in place. The traditional pathway of management has occurred "in series." The number of problems in this approach includes: lack of stratification, lack of early appreciation of AKI effects, reliance on a delayed marker of injury, and a paucity of options for treatment. A novel and more appropriate approach treats S-AKI "in parallel" (Fig. 6.5). Sepsis is treated but incorporated early in the algorithm for AKI risk stratification. Patients with high risk are delineated from those at low risk although both receive supportive care and an AKI prevention bundle (based on KDIGO management guidelines). The high-risk patients then have a series of tests done to phenotype their injury pattern including a panel of urine and serum biomarkers specific for timing, location, and mechanism of injury. A furosemide stress test is performed to determine tubular function and reserve. A real-time GFR monitor is placed to track filtration on a more constant basis and determine kinetic changes in GFR. A combination of these results yields specific, individual phenotypes for AKI or S-AKI. Targeted therapies are then instituted for the specific phenotypes.

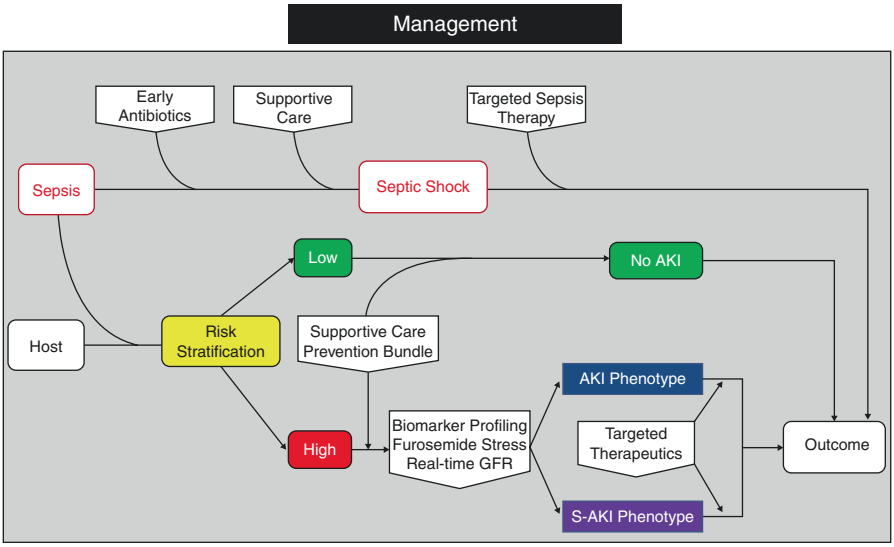

Fig. 6.5 Modern approach—management in parallel. Sepsis and AKI should be recognized and managed from the beginning, starting with appreciation of risk. The complexity of newer sepsis management strategies are not shown here but involve potential to target therapy based on sepsis signatures. Patients can be risk stratified for AKI and then assessed at an early stage, with concurrent supportive care and AKI prevention in place, using urinary and serum biomarkers and real-time outputs of glomerular and tubular function yielding specific phenotypes of injury. Targeted therapies (including early renal replacement therapy initiation) can be tested in this context and specific phenotype and therapy-based outcomes determined

6.1.9 Conclusion: The Path Forward

Sepsis-associated AKI is a significant problem in critically ill patients. The past and present paradigm of how this syndrome-like injury is understood needs to be changed, updated, and refined. An analytical, objective evaluation of the strengths and weaknesses of the S-AKI paradigm can be created using a "SWOT" (Fig. 6.6). The strengths of the current paradigm include, most importantly, a growing appreciation of the S-AKI, not just in the critical care and nephrology community. The weaknesses have been described in this chapter and cumulatively lead to a black box and one-size-fits-all approach S-AKI. Epidemiologic data from developing nations is infrequent yet sepsis and AKI are undoubtedly common in these parts of the world (notably Southeast Asia, most of sub-Saharan Africa, and Central America). This data is needed to fully understand the scope of disease. Opportunities exist and must be leveraged, including utilization of the electronic medical record (EMR) while simultaneously paying appropriate respect to factors that imperil progress (threats). Diagnostic modernization is possible with technology that currently exists and would lead to a more precise understanding of the disease. Ultimately, these combined approaches and efforts on all aspects of S-AKI disease should facilitate improvements in management and ultimately improve outcomes for patients of all ages.

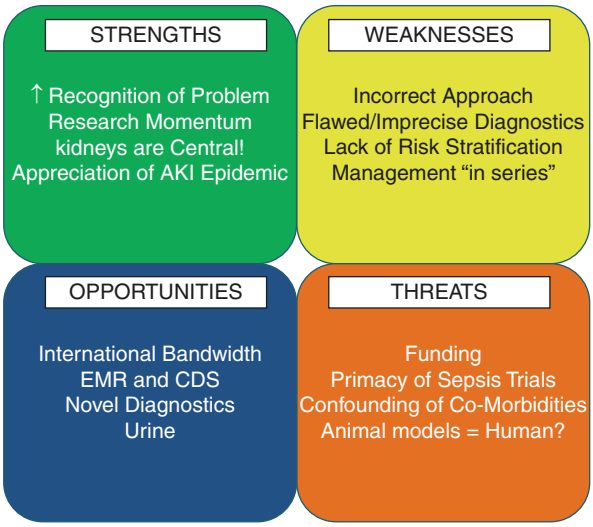

Fig. 6.6 Sepsis-associated AKI—A SWOT approach. Depicted above are the strengths (S), weaknesses (W), opportunities (O), and threats (T) in the past, present, and future paradigm of S-AKI. (*EMR* electronic medical record, *CDS* clinical decision support)

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